

REMARKS

Claims 1, 2, and 6 are pending in this application. By this Amendment, claim 6 is amended. Support for the amendment to claim 6 may be found, for example, in the specification at paragraphs [0036] and [0039]. No new matter is added.

Entry of the amendments is proper under 37 CFR §1.116 because the amendments: (a) place the application in condition for allowance (for the reasons discussed herein); (b) do not raise any new issue requiring further search and/or consideration; (c) satisfy a requirement of form asserted in the previous Office Action; (d) do not present any additional claims without canceling a corresponding number of finally rejected claims; and (e) place the application in better form for appeal, should an appeal be necessary. The amendments are necessary and were not earlier presented because they are made in response to arguments raised in the final rejection. Entry of the amendments is thus respectfully requested.

In view of the foregoing amendment and follow remarks, reconsideration and allowance are respectfully requested.

I. Finality of Rejection

Applicants respectfully noted in their January 22, 2009 response to the July 22, 2008 Office Action, that pursuant to a telephone conference held with Examiner Robinson on November 20, 2008, Examiner Robinson agreed that any next Office Action would be non-Final, in view of the fact that Applicants were not provided with the translation of JP 02011592 to Matsumoto et al. ("Matsumoto") until December 4, 2008. As a result of this delay, Applicants experienced prejudice in the timely preparation of a response to the Office Action. Accordingly, Applicants respectfully request that Examiner Robinson withdraw the finality of the present Office Action.

II. Rejections Under 35 U.S.C. §103

A. Sakoda and Brittain

The Office Action rejects claims 1, 2, and 6 under 35 U.S.C. §103(a) as having been obvious over the combination of Sakoda et al., *Synthesis and Crystal Structure of Optically Active 2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate(NZ-105)*, Chem. Pharm. Bull. 2377-2381 (1992) ("Sakoda") and Brittain, *Crystallographic Consequences of Molecular Dissymmetry*, Pharmaceutical Research, Vol. 7 (1990) ("Brittain"). Applicants respectfully traverse the rejection.

Claim 1 recites "dissolving a racemate of the compound of formula (1) in a solvent to prepare a supersaturated solution; and adding crystal of either one optically active substance of the compound of formula (1) as a seed crystal in the supersaturated solution to allow crystal of the one optically active substance added as the seed crystal to separate out." The combination of applied references do not disclose and would not have rendered obvious the claimed process for at least the following reasons.

The Office Action acknowledges that Sakoda at least does not disclose "dissolving a racemate of the compound of formula (1) in a solvent" (emphasis added). *See* page 2. The Office Action asserts, however, that Brittain discloses that the claimed process is a "conventional method of separating enantiomers from racemic mixtures" and further asserts that it would have been obvious to use the method disclosed by Brittain to produce the optically active compound disclosed by Sakoda. *See* page 3.

To the contrary, Brittain discloses that direct crystallization techniques are "necessarily limited to racemates which crystallize as conglomerates," and further discloses that conglomerate behavior is displayed only when the melting point of the resolved enantiomers is at least 20°C higher than the melting point of the racemic mixture, such that

only "about 5-10% of chiral crystalline compounds exist as conglomerates." *See* Brittain at page 686, column 2, lines 22-30 and page 687, column 2, lines 16-22.

Brittain discloses that a second type of racemic mixture, a true racemate, "is certainly the most commonly encountered type of racemic mixture." *See* Brittain at page 686, column 2, lines 36-39. Moreover, Brittain discloses that direct crystallization cannot be used to separate the enantiomers of a true racemic mixture. *See* Brittain at page 688, column 1, lines 30-32. Instead, Brittain concludes that "[t]rue racemates can be separated only after the performance of a derivatization reaction." *See* Brittain at page 688, column 1, lines 33-35.

Although the section "Resolution of Conglomerates" is a subheading of "RESOLUTION OF ENANTIOMER MIXTURES" in Brittain, Brittain discloses numerous methods for resolving various types of enantiomer mixtures. *See* Brittain at page 687, column 1, lines 55-61. As such, Brittain discloses that direct crystallization can be used to resolve enantiomer mixtures, but only those enantiomer mixtures that crystallize as conglomerates.

The Office Action asserts that Applicants do "not state in the specification or in the claims, that the claimed compound products can not be conglomerates." *See* page 5. Nonetheless, it would not have been obvious that resolution would have been achieved by direct crystallization because the possibility that a racemic mixture exists as a conglomerate is much smaller than the possibility that the racemic mixture exists as a true racemate.

Brittain must be considered in its entirety, "including portions that would lead away from the claimed invention." *See* MPEP §2141.03. The direct crystallization process of Brittain is applicable only for conglomerates, which exist only rarely. Thus, an ordinarily skilled artisan would not have had a reasonable expectation of success of achieving the claimed method in view of the teachings of Sakoda and Brittain.

Moreover, the direct crystallization process disclosed by Brittain requires the preparation of a solution that contains an excess of one enantiomer in which the ratio is 62.6 to 37.4 before adding the mixture to a solvent. *See* Brittain at page 687, column 2, lines 52-53. Specifically, Brittan describes an "excellent example" of the direct crystallization process in which 1100 mg of racemic hydrobenzoin is dissolved along with 370 mg of (-)-hydrobenzoin in a solvent. *See* Brittain at page 687, column 2, line 59 to page 688, column 1, line 3. As such, Brittain does not disclose "dissolving a racemate" in a solvent, but discloses dissolving an excess of one enantiomer in a solvent.

On the other hand, the claimed process can be carried out by adding only 1 wt% of the seed crystal to the racemate, which results in a 51 to 50 ratio. *See* specification at paragraphs [0035]- [0040] (Examples 1-5). From this ratio, a crystal having a ratio of 94 to 6 is produced in Example 1 (and a mother liquid having a ratio of 43 to 57 is produced). In Examples 2-4, crystals having ratios of 56 to 44, 76 to 24, and 96.5 to 3.5 are produced, respectively, (and mother liquids having ratios of 48 to 52, 42 to 58, and 55 to 45 are produced, respectively). In Example 5, more than 1 g of the optically active substance of the compound of formula (1) can be produced in turn starting from 5 g of racemate and 50 mg of the seed crystal by adding the same weight of the racemate as the enantiomer precipitated along with 50 mg of a highly purified enantiomer. Thus, the claimed method is superior to the "excellent example" disclosed by Brittain.

Accordingly, the combination of Sakoda and Brittain would not have rendered obvious claim 1. Claims 2 and 6 depend from claim 1 and, thus, also would not have been rendered obvious by the applied references for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Matsumoto and Brittain

The Office Action rejects claims 1, 2, and 6 under 35 U.S.C. §103(a) as having been obvious over the combination of Matsumoto and Brittain. Applicants respectfully traverse the rejection.

The Office Action acknowledges that Matsumoto, like Sakoda, fails to disclose "dissolving a racemate of the compound of formula (1) in a solvent to prepare a supersaturated solution." *See* page 4. The Office Action asserts, however, that Brittain cures the deficiencies of Matsumoto.

The deficiencies of Brittain with respect to claim 1 are discussed above. Thus, the combination of Matsumoto and Brittain would not have rendered obvious claim 1. Claims 2 and 6 depend from claim 1 and, thus, also would not have been rendered obvious by the applied references for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of this application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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Attachment:
Petition for Extension of Time

Date: August 17, 2009

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